REMARKS

Reconsideration is requested.

Claims 3-5, 7-8, 14, 17-19, 25, 29, 33-35, 42-47, 49, 52-54, 59-61 and 63-66 have been canceled, without prejudice. Claims 1, 2, 6, 9-13, 15-16, 20-24, 26-28, 30-32, 36-41, 48, 50-51, 55-58 and 62 are pending.

The Examiner is requested to reconsider the restriction requirement in so far as claim 62 was included in the Examiner's Group II. The applicants submit that claim 62 should be included in the elected Group I, especially in light of the Examiner's comments on pages 8-11 of the Office Action dated January 13, 2005. Examination and allowance of claim 62 are requested.

The specification has been amended to include the attached formal drawings. Acceptance of the attached formal drawings and withdrawal of the objection to the figures stated on pages 2-3 of the Office Action dated January 13, 2005, are requested.

The objection of claim 63 stated on page 3 of the Office Action dated January 13, 2005, is moot in view of the above.

The Section 112, second paragraph, rejection of claims 1-41, 48-58 and 63-66 is obviated by the above amendments. The applicants submit the following in response to the Examiner's lettered paragraphs:

a. The claims refer to (an) antibody conjugate as opposed to the term objected-to by the Examiner. Moreover, one of ordinary skill in the art will appreciate that claim 1, for example provides an antibody conjugate of a monoclonal antibody with a protein or a lower molecular weight agent.

b. Claim 1 is submitted to clearly define that the protein or the low molecular weight agent is not conjugated with a ganglioside GD3 but with a monoclonal antibody.

c. Claim 14 has been canceled, without prejudice.

d. Claims 63 to 66 have been canceled, without prejudice.

e. Claim 7 has been canceled, without prejudice.

f. Claims 7 and 64-66 have been canceled, without prejudice. Claim 48 recited "a humanized antibody", which is submitted to be definite..

g. Claims 1 and 48 recite "binds to", which is submitted to be definite.

Withdrawal of the Section 112, second paragraph, rejection of claims 1-41, 48-58 and 63-66 is requested.

The Section 112, first paragraph, rejection of claims 6, 13 and 23 stated on pages 6-11 of the Office Action dated January 13, 2005, is obviated by the above amendments and the following.

The applicants confirm that the deposit of hybridoma KM-641 and cell clones producing antibodies KM-871 and KM-8871 have been accepted by an International Depository Authority under the provisions of the Budapest Treaty (see, attached copies of the Deposit Receipts), and that all restrictions upon public access to the deposited material will be irrevocably removed upon the grant of a patent on this applications in the event the claims recite the deposited material.

Withdrawal of the Section 112, first paragraph, rejection of claims 6, 13 and 23 is requested.

The Section 112, first paragraph, rejection stated on pages 11-14 of the Office Action dated January 13, 2005, is obviated by the above amendment. Withdrawal of the rejection is requested.

Certified English language translations of the priority documents will be filed under separate cover.

The Section 102 rejection of claims 1-2 and 64-66 over Chapman (Cancer Research, 50:1503-1509, March 1, 1990), is obviated by the inclusion of the details of novel claims 5 or 54 in the rejected claims. Withdrawal of the Section 102 rejection is requested.

Similarly, the Section 103 rejection of claims 1-2, 7-9, 14-16, 24-25, 36-37, 48-51 and 63-66 over the combination Chapman, Queen (U.S. Patent No. 5,530,101), and LeBerthon (Cancer Research, 51:2694-2698, 1991), is obviated by the above amendments and withdrawal of the rejection is requested.

The following Section 103 rejections are traversed:

The Section 103 rejection of claims 1-19, 24-29, 33-39, 48-54 and 63-66 over Hanai (Cancer Chemotherapy and Pharmacology, 46 (Suppl):S13-S17, June 2000) "as evidenced by" Shitara (EP 0533199 A2) in view of Queen and Nakamura (Cancer, 80(12 Suppl):2650-2655);

The Section 103 rejection of claims 1-19, 24-29, 33-39, 48-54 and 63-66 over Shitara, Queen and Nakamura;

The Section 103 rejection of claims 1-19, 24-29, 33-39, 48-54 and 63-66 over Shitara in view of Queen and Nakamura; and

The Section 103 rejection of claims 1-19, 24-29, 33-39, 48-54 and 63-66 over Shitara in view of Queen and Nakamura.

Reconsideration and withdrawal of the rejections are requested in view of the following distinguishing comments.

Claim 1, for example, provides an antibody conjugate, comprising a monoclonal antibody or an antibody fragment thereof which specifically binds to GD3 and comprises VHs represented by SEQ ID NOs:3-5 and VLs represented by SEQ ID NOs:6-8.

The Examiner is understood to assert that it would have been obvious to produce an antibody conjugate of KM871 and IL-2, *etc.* in order to enhance therapeutic benefit based on Hanai, et al. However, even if the general production of an antibody conjugate was obvious, which the applicants do not concede, it was not predictable from the cited art that an antibody conjugate of KM871, for example, would retain the antibody properties of the original unconjugated antibody.

Generally, when an antibody conjugate is produced by binding an antibody to any molecule, the three-dimensional structure of the antibody is changed so that the properties of the antibody, such as antigen binding activity, antigen specificity and cytotoxic activity, are often changed. According to the attached Presentini et al (*Journal of Immnoassay*, 16(3), 309-324 (1995)), a conjugate must meet certain criteria of sensitivity, specificity and stability (see page 309, last 3 lines). That is, it is shown that when an antibody conjugate is produced, the antigen binding activity and antigen specificity of the antibody conjugate must be examined.

Furthermore, in TABLE 1 of the attached Nakamura et al (*CANCER Supplement*, 80, 2650-2655 (1997)), the antigen binding activities are compared in antibody

conjugates of an antibody with IL-2 or a radioisotope. The binding activity of the antibody conjugate of the antibody with the radioisotope is 90-100% of the original antibody, whereas the antibody conjugates of the antibody with IL-2 have 10-40% lowered binding activity.

Thus, when an antibody conjugate is produced by conjugating an antibody to any molecule, it was the common technical knowledge at the time the present application was filed that the antibody activity, such as the antigen binding activity, may be changed, and that the produced antibody conjugate will not always retain the activity of the original antibody.

The antibody conjugate of the present invention retained the antigen binding activity and antigen specificity of the original antibody alone as shown in the items 2.(1) and (2) in Example 3 (see Figs. 32 to 34). Also, the cytotoxic activity of the antibody conjugate was significantly increased in comparison with that of the antibody alone (see Fig. 36). These aspects of the claimed invention were not predictable from the cited art.

Also, as shown in Example 1, the antibody conjugate of the present invention had a little changed antigen specificity in comparison with the antibody alone (Fig. 26). On the other hand, the binding activity against an antigen, ganglioside GD3, was improved (Fig. 25), and the reactivity to GD3-expressing cells was not changed (Fig. 27). Furthermore, the cytotoxic activity was significantly increased in comparison with that of the antibody alone (see Fig. 29) in the same manner as the above antibody conjugate.

Moreover, regarding *in vivo* effects, administration of the antibody conjugate of the present invention provided an improved anti-metastatic effect as compared with

administration of an anti-GD3 chimeric antibody alone or administration in combination of IL-2 with an anti-GD3 chimeric antibody (Tables 3 to 5 and Figs. 39 to 41). In the solid tumor early model and advanced stage model, administration of the antibody conjugate of the present invention provided a greater anti-tumor effect and greater life-prolonging effect than administration of an anti-GD3 chimeric antibody alone or administration in combination of IL-2 with an anti-GD3 chimeric antibody (Tables 6 to 11 and Figs. 43 to 44).

Accordingly, the antibody conjugate of the present invention has improved cytotoxic activity without changing the binding activity of the antibody. The antibody conjugate also has unexpectedly improved and/or enhanced properties which would not have been from the cited art.

Claim 48, for example, relates to a humanized antibody or the antibody fragment thereof which specifically binds to ganglioside GD3 and comprises VH having the amino acid sequence represented by SEQ ID NO:9 or the amino acid sequence in which at least one or more amino acid residue selected from 10th position Gly, the 11th position Leu, 20th position Leu, 28th position Thr, 84th position Asn, 91st position Thr, 95th position Tyr, 97th position Ala and 115th position Val in the amino acid sequence represented by SEQ ID NO:9 is replaced with another amino acid residue; and VL having the amino acid sequence in which at least one or more amino acid residue selected from 49th position Tyr, the 65th position Ser and 71st position Phe represented by SEQ ID NO:10 is replaced with another amino acid residue.

As described at page 59, line 30 to page 60, line 13, in the production of the humanized antibody, the activity of the antibody is often reduced by only grafting of a

non-human antibody CDR amino acid sequence alone. Thus, in order to avoid the reduction of the antigen binding activity of antibodies, framework (FR) amino acid residues considered to be exerting influences on the antigen binding activity were grafted together with a CDR amino acid sequence.

As described at page 60, line 14 to page 61, line 24, the three-dimensional structure analysis was carried out for the humanized antibody in which KM641 is grafted as the base of the humanized antibody, and CDRs of the heavy chain and light chain variable regions of KM641 were grafted to the framework of a human antibody. Specifically, the humanized antibody comprises the amino acid sequence represented by SEQ ID NO:9 and the amino acid sequence represented by SEQ ID NO:10. As a result, it was found that the 0th position Gly, the 11th position Leu, the 20th position Leu, the 28th position Thr, the 84th position Asn, the 91st position Thr, the 95th position Tyr, the 97th position Ala and the 115th position Val in the amino acid sequence represented by SEQ ID NO:9 were replaced with another amino acid residue; and VL having the amino acid sequence in which at least one or more amino acid residue selected from the 49th position Tyr, the 65th position Ser and the 71st position Phe represented by SEQ ID NO:10 were amino acid residues considered to be exerting influences on the antigen binding activity. The humanized antibody can be produced by grafting at least one of these amino acid residues considered to be exerting influences on the antigen binding activity together with CDR of KM641. The chimeric antibody KM871 thus produced has binding activity to GD3 (Figs. 14 and 15), reactive specificity against various gangliosides (Fig. 16) and binding activity to GD3 expressing cell (Fig. 17), each similar to the activity of chimeric antibody KM871.

None of the cited references disclose or suggest the amino acid residues in framework (FR) amino acid residues in the heavy chain and the light chain, which amino acids are considered to be exerting influences on the activity of the antibody as described above. Accordingly, the humanized antibody of the present invention, which retains the antigen binding activity, was not expected to be produced by one of ordinary skill in the art with any predictability. Accordingly, the humanized antibody of the present invention would not have been obvious from the cited art and withdrawal of the Section 103 rejections is requested.

The Examiner is requested to hold the following rejections in abeyance until such time that allowable subject matter is identified:

The rejection of claims 1-19, 24-29, 33-39, 48-54 and 63-66 under the judicially created doctrine of obviousness-type double patenting over claims 1-4 of U.S. Patent No. 6,437,098 "in view of Queen and Nakamura";

The rejection of claims 1-19, 24-29, 33-39, 48-54 and 63-66 under the judicially created doctrine of obviousness-type double patenting over claims 1-2 of U.S. Patent No. 5,750,078 "in view of" Shitara (EP 0533199), Queen (U.S. Patent No. 5,530,101) and Nakamura; and

The rejection of claims 1-19, 24-29, 33-39, 48-54 and 63-66 under the judicially created doctrine of obviousness-type double patenting over claims 1-2 of U.S. Patent No. 6,495,666 "in view of" Shitara, Queen and Nakamura.

The applicants will consider whether a Terminal Disclaimer is appropriate once allowable subject matter is identified.

The applicants confirm that inventions of the present application and the claims of U.S. Patent Nos. 6,437,098; 5,750,078 and 6,495,666 were commonly owned at the time of the invention of this application. Withdrawal of the following rejections is therefore requested:

claims 1-19, 24-29, 33-39, 48-54 and 63-66 as allegedly not being patentably distinct from claims 1-4 of U.S. Patent No. 6,437,098;

claims 1-19, 24-29, 33-39, 48-54 and 63-66 as allegedly not being patentably distinct from claims 1-2 of U.S. Patent No. 5,750,078; and

claims 1-19, 24-29, 33-39, 48-54 and 63-66 as allegedly not being patentably distinct from claims 1-2 of U.S. Patent No. 6,495,666.

The claims are submitted to be in condition for allowance and a Notice to that effect is requested.

Return of an initialed copy of the attached PTO-1449 Form, pursuant to MPEP § 609, is requested.

Respectfully submitted,

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IN THE FIGURES

Amend the figures by inserting the attached 41 sheets of formal drawings for the originally-filed 41 sheets of informal drawings.